Published in final edited form as:
Drug Alcohol Depend. 2014 June 1; 139: 93–99. doi:10.1016/j.drugalcdep.2014.03.007.

Substance Use Patterns and Factors Associated with Changes Over Time in a Cohort of Heterosexual Women At Risk for HIV Acquisition in the United States

Irene Kuo[1], **Carol E. Golin**[2], **Jing Wang**[3], **Danielle F. Haley**[4,5], **James Hughes**[3,6], **Sharon Mannheimer**[7,8], **Jessica Justman**[8], **Anne Rompalo**[9], **Paula M. Frew**[5,10], **Adaora A. Adimora**[2], **Lydia Soto-Torres**[11], **Sally Hodder**[12], and **for the HPTN 064 Study Team**

[1]George Washington University School of Public Health and Health Services, Washington, DC

[2]University of North Carolina Schools of Medicine and Gillings School of Global Public Health, Chapel Hill, NC

[3]Fred Hutchinson Cancer Research Center, Seattle, WA

[4]FHI 360, Durham, NC, USA

[5]Rollins School of Public Health, Department of Behavioral Sciences and Health Education, Atlanta, GA, USA

[6]Department of Biostatistics, University of Washington, Seattle, WA

[7]Harlem Hospital Center, New York, NY

[8]Mailman School of Public Health, Columbia University, New York, NY

[9]Johns Hopkins University School of Medicine, Baltimore, MD

[10]Emory University, Department of Medicine, Division of Infectious Diseases, Atlanta, GA, USA

[11]National Institutes of Health, National Institute on Allergy and Infectious Diseases, Bethesda, MD

[12]Rutgers, New Jersey Medical School, Newark, NJ

Abstract

Correspondence: Irene Kuo, George Washington University, School of Public Health and Health Services, Department of Epidemiology and Biostatistics, 2100-W Pennsylvania Avenue NW, 8th Floor, Washington, DC 20037, Phone: 202-994-0367 Fax: 202-994-0082, ikuo@gwu.edu.

Contributors: IK was responsible for conceiving the idea, interpreting the analysis, and writing the manuscript; CG, DH, SM, JJ, AR, PF, AA, LS and SH were responsible for helping to conceive the idea, interpreting the analysis and editing the manuscript; JW and JH were responsible for conducting the data analysis, interpreting the analysis and editing the manuscript.

Conflict of Interest: No conflict declared.

Background—Substance use is associated with HIV sexual risk behaviors, yet few studies have examined substance use patterns longitudinally. We evaluated the types and frequency of substances used over a six-month period among U.S. women at risk for HIV acquisition.

Methods—Women reporting unprotected sex with a man in the previous six months and at least one other personal or partner HIV risk characteristic enrolled in a multisite cohort study and completed interviews about substance use at study visits. Prevalence and frequency of substance use at the baseline and six-month visits were compared and correlates of decreased substance use at the six-month visit were assessed.

Results—Of 2,099 women enrolled, 1,882 had substance use data at baseline and six-months. Of these, 76.1% reported using at least one drug or binge drinking in the previous six months; 37.5% were frequent and 38.6% non-frequent substance users. Binge drinking was most frequently reported (63.3%), followed by cocaine (25.0%) and opioids (16.5%). Fifty-five percent of opiate users and 30% of cocaine users reported daily/almost daily use. At the six-month visit, 40.5% reported a decrease in frequency of use. Adjusting for income and type of drug used, poly-substance users were less likely to decrease frequency of use compared to those who only used one substance.

Conclusion—A substantial decrease in frequency of substance use over time was observed in this cohort. Poly-substance users were less likely to reduce frequency of use over time, suggesting that specific substance use interventions targeting these users are warranted.

Keywords

women; substance use; opiate use; cocaine use; binge drinking; HIV

1. Introduction

In 2010, 28% of all newly reported HIV cases nationally were attributed to heterosexual transmission (Centers for Disease Control and Prevention (CDC), 2012a). Among women, the vast majority of reported cases (86%) were attributed to heterosexual sex (CDC, 2012a). Significant racial disparities also exist for newly reported cases among women. Of the total number of new HIV infections among women in the United States in 2010, 64% occurred in blacks/African Americans, more than three times that of white women (18%; CDC, 2013. Similarly, the overall new case rate per 100,000 for the general female adult and adolescent population is 8.0 per 100,000, yet the rate for black/African-American women is 41.7 per 100,000, nearly 20 times as high as white females (2.1 per 100,000) and approximately four and half times as high as Hispanic/Latino females (9.2 per 100,000; CDC, 2012b).

Substance use (both drugs and alcohol) has been consistently found to be associated with risky sexual behaviors (Hutton et al., 2012; Patrick et al., 2012; Stein et al., 2005), including concurrent sexual partnerships (Adimora et al., 2003, 2011) and low or no condom use (Ober et al., 2011; Patrick et al., 2012), as well as sexually transmitted infections, including HIV (Edlin et al., 1994; McClelland et al., 2007; Nijhawan et al., 2011; NIMH Multisite HIV/STD Prevention Trial for African American Couples Group, 2010; Seth et al., 2011; Sterk et al., 2003; Van Der Pol et al., 2008). Low income has been found to be associated with elevated prevalence of viral infections and HIV (Dinenno et al., 2012; Stover et al.,

2003), and research on neighborhood characteristics and substance misuse suggests a positive association between economic disadvantage and the use of alcohol and other drugs (Boardman et al., 2001; Cohen et al., 2003; Jones-Webb et al., 1997; Theall et al., 2009; Williams et al., 2007).

Although much research has studied substance use among women at high risk for HIV infection, few have examined changes in substance use over time and the factors that drive those changes. Several studies examining substance use behaviors among women at high risk for HIV have been conducted within the Women's Interagency HIV Study (WIHS) cohort. Baseline data from WIHS revealed a high prevalence of drug use, with 28.9% of cohort participants reporting drug use in the previous six months, and among those who were HIV-negative, 25% reported crack use, 19.7% reported cocaine use, and 10.3% reported injection drug use at baseline (Wilson et al., 1999). Two studies of longitudinal patterns of drug use were conducted using WIHS data, but both focused on marijuana use, and one was conducted among HIV-positive participants only (D'Souza et al., 2012; W. H. Kuo et al., 2004). In a different longitudinal study, Warner et al. found that among crack and cocaine using women in Puerto Rico, those who traded sex for money and exhibited depressive symptoms were less likely to experience remission of drug dependence symptoms (Warner et al., 2004). This study, however, was limited by its small sample size and lack of broader generalizability beyond its one unique geographic location. Therefore, there is a need to assess more complex substance use patterns, changes in the frequency of use over time, or the factors that may be driving these changes within a geographically diverse group of women at risk for HIV.

We examined data from the HIV Prevention Trials Network (HPTN) 064 The Women's HIV SeroIncidence Study. The purpose of HPTN 064 was to evaluate HIV incidence among US women living in geographic areas with high rates of poverty and HIV prevalence and to assess factors that may increase HIV acquisition risk. HIV annual incidence in the HPTN 064 cohort (consisting of predominantly African American women) was 0.32% (Hodder et al., 2013), nearly six-fold higher than that estimated for the general population of African American women of similar age (Prejean et al., 2011). Baseline substance use was found to be significantly associated with baseline HIV infection in HPTN 064 (Hodder et al., 2013).

The objective of this study was to analyze substance use patterns in a large, geographically diverse cohort of women at increased risk for HIV acquisition. We examined the types and frequency of substances used in the baseline cohort and the changes in the frequency of use and factors associated with decreased substance use during the first six months of the HPTN 064 study.

2. Methods

2.1 Study Design

As previously described (Hodder et al., 2013), HPTN 064 was a multi-site, longitudinal cohort study enrolling women between May 2009 and July 2010. The study sample was drawn from 10 urban and peri-urban communities with a high prevalence of poverty and HIV prevalence located in the Northeastern and Southeastern US. Previous descriptions of

the locations and sampling strategy have been published elsewhere (Hodder et al., 2013). Approximately 210 women were recruited from each community. Venue-based sampling was used to recruit women who attended specific locations within defined geographic areas. In brief, index scores for census tracts in the 10 communities were developed using an algorithm including poverty rate based on census data and/or zip codes (used in New York City) and HIV/AIDS prevalence based on local public health surveillance data. We identified the venues in the top 30% ranking census tracts that are frequented by women who potentially would be eligible to participate. Venues and corresponding recruitment times were randomly selected each month; women were approached systematically at these venues to be screened for study eligibility. Eligible individuals resided in these identified census tracts/zip codes, were 18 to 44 years of age, self-identified as a woman, reported at least one episode of unprotected vaginal and/or anal sex with a man in the six months before enrollment as well as an additional personal or partner HIV risk characteristic, and were willing to undergo HIV rapid testing and receive HIV test results. Women were followed for six or 12 months, depending on time of enrollment, as previously described (Hodder et al., 2013). The HPTN 064 study was approved by institutional review boards at all study sites and collaborating institutions. A Certificate of Confidentiality was obtained for the study.

Participants underwent HIV testing and audio computer-assisted self-interviews (ACASI) at entry to the study and at six-month intervals for up to 12 months. The baseline and six month ACASI, which collected self-reported demographic, behavioral (sexual and substance use behaviors) and psychosocial data, were the data sources for this analysis. Sexual risk behaviors assessed included number of sexual partners in the last six months, condom use, exchange of sex for money, drugs and/or goods/services, and self-reported direct concurrency, which was defined as the participant reporting that she had overlapping sexual partnerships in the past six months. Other behaviors and experiences included incarceration for at least 24 hours within the previous five years, depressive symptomatology (assessed using the CES-D-8, in which a score of ≥7 of 32 on an eight-item four point scale was positive for depressive symptoms) (DiClemente et al., 2001; Melchior et al., 1993) and post-traumatic stress disorder (PTSD) using the four-question Primary Care PTSD screener (Prins et al., 2003), in which a score ≥3 (at least three out of four) suggested an increased likelihood of a PTSD diagnosis. Incarceration history was assessed through an eligibility screener prior to enrollment.

2.2 Definition of Substance Use

Self-reported substance use (drug use and/or binge drinking) in the previous six months was assessed using a modified World Health Organization ASSIST scale (World Health Organization ASSIST Working Group, 2002). Past six-month use of substances was assessed individually and included: alcohol (binge drinking defined as four or more drinks in one sitting), opioids, cocaine, amphetamine-type stimulants, inhalants, sedatives/sleeping pills, and hallucinogens. Cannabis use was assessed, but due to lack of evidence regarding its association with HIV risk (Logan et al., 2000; Smith et al., 2010), it was excluded from this analysis. Based on major subclasses of drugs identified by Friedman (Friedman et al., 2003) and distribution of use across the sample, we defined six hierarchical and mutually exclusive categories of substance use as (from highest to lowest level of HIV riskiness) 1)

opioid use; 2) cocaine use (including crack and powdered cocaine); 3) amphetamine use; 4) sedative/sleeping pill use; 5) use of inhalants, hallucinogens, or other drugs; and 6) binge drinking. For example, if a participant reported using opioids and amphetamines, she would be classified as being an opiate user, which is the higher of the two risk categories. We applied a similar hierarchical substance use categorization in a previous study (Kuo et al., 2011).

The prevalence of use in the past six months was calculated for each of the six substance categories for the total study population. We assessed the use of multiple substances during the recall period in two different ways. To present information on the types (versus number) of drugs used during the recall period, for each drug class, we calculated the proportion of individuals who used each of the other classes of substances (e.g., of opioid users, 66.1% also used cocaine), as has been done previously (Kuo et al., 2011). In addition, a more conventional presentation of the use of multiple substances is presented as the number of different substances a participant reported using in the previous six months, categorized as either one, two, three or four or more substances used.

2.3 Frequency of substance use

For this analysis, only women who reported using any substance (excluding cannabis) at baseline were included. For each substance used during the prior six months, substance use frequency was categorized as 1) daily to less than weekly, 2) weekly, 3) monthly or 4) once or twice (<monthly). The substance most frequently used by a woman in the previous six months was considered the “drug of choice” and was used to categorize each person regarding drug use frequency. Therefore, individuals who used more than one substance were categorized based on the drug used most frequently during the recall period. If an individual reported using multiple drugs at the same frequency, then a decrease in frequency of any of the drugs reported was counted as a decrease in frequency.

To assess changes in substance use frequency between baseline and the six month study visit, the frequency of substance use was further collapsed and categorized as 1) frequent substance use (defined as daily to weekly use of any illicit drug and/or weekly binge drinking); 2) non-frequent substance use (defined as less than weekly use of illicit drugs and/or monthly binge drinking); 3) non-use (those who did not use any illicit drugs or binge drink). Since only women who used drugs at baseline were included in this analysis, the non-use category is applicable at the six month follow-up visit only. The frequency of drug use was compared across the two visits. Individuals were categorized as decreasing substance use if their frequency changed from frequent to non-frequent use or to no substance use. Individuals with non-frequent substance use at baseline who reported no substance use at the six-month visit were also categorized as decreased substance use. All others including those who used at the same frequency or increased their usage frequency were categorized as not having decreased substance use.

2.4 Data analysis

Data analysis was conducted in three phases. First, descriptive characteristics were calculated and presented by frequency of drug use for the entire study population, including

those who did not use drugs. Second, to describe the extent of multiple substances used in the sample, the prevalence of substance use and poly-substance use was calculated based on the aforementioned hierarchical categorization among the women who reported any substance use at baseline. Third, we calculated the proportion of women who reported decreased substance use from baseline to the six month follow-up visit. Bivariate log regression and relative risks were used to describe baseline predictors associated with decreased substance use over time. Multivariable log regression analysis was conducted adjusting for all variables significant at $p<0.10$ in the bivariate analyses. Variables attaining $p\leq0.05$ were retained in the model and considered to be statistically significant. All analyses were conducted using SAS version 9.2 (SAS Inc., NC).

3. Results

Of the 2,099 women enrolled, 89.7% (n=1,882) had complete data on substance use at the baseline and six-month visits. Of these, 23.9% did not report using any substances at the baseline visit, while 76.1% (n=1,432) reported using at least one of the substances or binge drinking in the previous six months, of which 37.5% were frequent substance users and 38.6% were non-frequent substance users (Table 1). Compared to non-frequent users and non-users, frequent substance users were significantly older, less educated and earned less money. Frequent users were also more likely to have had more than one sex partner in the past six months, reported concurrent partnership, had a male partner who used drugs, had anal sex, and exchanged sex for commodities in the past six months. These women were also more likely to have been incarcerated, report depressive symptoms, and screen positive for PTSD.

The most prevalent substance used was alcohol, with 63.3% of the study population reporting binge drinking in the six months prior to enrollment, followed by cocaine use (25.0%) and opioid use (16.5%; Table 1). Approximately one in ten women reported using amphetamines (10.8%). Nearly the same proportion used sedatives/sleeping pills (10.1%). The prevalence of opioid and cocaine, sedative/sleeping pill, and inhalant, hallucinogen or other drugs was higher among frequent users versus non-frequent users. However, the prevalence of binge drinking among the non-frequent users was higher compared to frequent users, although it was high in both groups (86.4% versus 79.9%, p=0.002). Frequent users were also significantly more likely to report using more than one substance than non-frequent users (62.9% versus 24.8%, p=<.0001). Of the women included in this analysis, overall 43%b reported using only one substance in the past six months at baseline, while more than one-third reported using two or more substances during that time period.

Table 2 describes the use of multiple substances across the different substance use groups reported at baseline. Among the women who reported using any substances in the six months prior to enrollment, 66% of opioid users also reported using cocaine, and 33% reported using sedatives or sleeping pills. Among those who used cocaine, 44% also used opioids, 24% used sedatives or sleeping pills, and 15% used amphetamines. Overall, the prevalence of binge drinking was high across each of the drug use groups, ranging from 56% among opiate users to 84% among amphetamine users. Opiate users reported the highest frequency of illicit substance use, with 54.5% of opiate users reporting daily or

almost daily opiate use, compared with only 30% of cocaine users reporting daily cocaine use. In contrast, the majority of amphetamine users (60.1%), sedative/sleeping pill users (44.2%) and inhalant/hallucinogen users (40.7%) used only once or twice in the past six months. Frequency of binge drinking was somewhat evenly distributed, with most binge drinkers (36.0%) reporting binge drinking only once or twice in the past six months, compared with 13.5% who reported daily or almost daily binge drinking.

At the six-month visit, 40.5% of those who reported any substance use at baseline reported a decrease in the frequency of use of the substance most frequently used at baseline, versus 59.5% who did not report a decrease in use (Table 3). On a bivariate level, individuals who decreased the frequency of substance use over time were more likely to have earned $10,000 or less at baseline (relative risk [RR]: 1.28; 95% confidence interval [CI]: 1.00, 1.63), although this was borderline statistically significant. Opioid users were less likely to decrease their frequency of substance use over time versus non-opioid users (RR: 0.86; 95% CI: 0.73, 1.01), which was also marginally statistically significant. Individuals who reported using four or more substances at baseline were significantly less likely to report a decrease in the frequency of use compared to those who only reported using one substance (RR: 0.72; 95% CI: 0.53, 0.97). Other characteristics, such as demographics, sexual behaviors, incarceration history, depression and PTSD were not significantly associated with decreased substance use over time. In the multivariable regression model, the number of substances used at baseline was the only independent predictor of reducing frequency of use: those who used two substances or four or more substances were less likely to reduce their substance use frequency compared to those who only used one (aRR=0.64 (0.42, 0.98) and aRR=0.22 (0.05, 1.00), respectively), adjusted for income and type of substance used.

4. Discussion

In this cohort of community-recruited women from areas of high HIV/AIDS case prevalence and poverty, a high prevalence of drug and alcohol use was observed. The prevalence of substance use in this study is much higher than national estimates of drug use and alcohol consumption in the general U.S. population (Compton et al., 2007; Hasin et al., 2007) and, in part, may reflect the study's inclusion criterion of substance use in the past six months. Our estimates are comparable, however, to cross-sectional estimates from other studies of US women at risk for HIV, including those using similar recruitment methods, after excluding binge drinking (Jenness et al., 2010; Lillie-Blanton et al., 2010; Richards et al., 2008; Wilson et al., 1999). Alcohol, specifically binge drinking, was the most prevalent substance used in our study, with nearly two-thirds of women reporting binge drinking in the six months prior to enrollment and, among these, more than one-third reported binge drinking on a daily to weekly basis. The estimate of binge drinking in our study far exceeds the prevalence (21%) estimate among rural African-American and Hispanic women in the Southeast US (McLellan-Lemal et al., 2012), and exceeds estimates reported in studies of women at risk for HIV using similar recruitment methods as part of National HIV Behavioral Surveillance (Jenness et al., 2010; Neaigus et al., 2012). Binge drinking is associated with high risk sexual behaviors related to HIV transmission, such as inconsistent condom use (Richards et al., 2008); and unprotected anal intercourse (McLellan-Lemal et al., 2012), suggesting the women in our study are also at risk for HIV due to high prevalence

of reported binge drinking. As reported previously (Hodder et al., 2013), formal statistical assessment of binge drinking as a predictor of HIV incidence in our study was not possible due to the small number of incident cases.

In addition, a substantial decrease in the frequency of substance use over time was observed. Women who used multiple substances were less likely to reduce their substance use frequency during the follow-up period. The use of multiple substances may suggest a higher level of dependence compared to those who use only one substance; this in turn may explain the lower likelihood of reducing substance use frequency over a six month period among poly-substance users. In a longitudinal study among low-income cocaine and crack using women in Puerto Rico, a similar decrease in drug dependence symptoms was also seen over a similar time period (Warner et al., 2004). However, the factors negatively associated with remission of drug dependence symptoms in that study (trading money for sex or drugs, depressive symptoms and drug abuse treatment (Warner et al., 2004)) differed from our study, in which using more than one substance was the only independent factor associated with frequency of use; these differences may be a result of geographic differences or differences in measures of reduced substance use. Remission of alcohol and drug use can occur spontaneously or with engagement in drug or substance use treatment; our study did not assess treatment experience during the follow-up period, which could have explained the decrease in use observed in our population. Low income was also associated with a decrease in frequency of use, suggesting that economic reasons may be driving the behavior change as has been seen in previous research (Corman et al., 2005; Dave, 2006); however, we were unable to explain this further since our study was not designed to explore the role of personal resource constraints on substance use behavior.

Other potential explanations for the decrease observed in this cohort include exposure to HIV pre- and post-test counseling, access to educational prevention materials, and receipt of referrals to local resources and care, including substance abuse treatment programs, as part of the study protocol. Although HPTN 064 was not an intervention-based study, perhaps exposure to HIV prevention messaging precipitated the decrease in actual or self-reported use. In addition, it is also plausible that because the baseline of substance use frequency was high from the start, part of the decrease observed could be attributed to a “regression to the mean” (Campbell et al., 2007). Alternatively, participants may have under-reported substance use at the follow-up visits due to socially-desirable reporting. Study staff conducted monthly check-in calls to support retention efforts for the study and were able to develop a close rapport with many of the study participants, which may have driven the desire to report more positive behaviors or acted as an intervention in itself. However, the use of ACASI for data collection likely mitigated some of this bias, (Macalino et al., 2002; Metzger et al., 2000), and therefore it is difficult to determine whether socially-desirable reporting is a true explanation for this decrease in substance use frequency.

Other limitations to this study should be noted. Although we used a standardized measure of substance use, substance abuse and dependence was not formally assessed, and it was not possible to determine whether these declines in substance use frequency would be reflected as changes in actual abuse/dependence status. In addition, due to lack of sample size for

subgroup analyses, we were unable to examine substance use trajectories within separate categories of substance use (i.e., opiate users versus cocaine users).

There were also several strengths in this study. First, this is the first longitudinal study to our knowledge that has focused on decreases in the frequency of substance use, rather than cessation or remission from drug use. Although one may argue that the ultimate goal of recovery from substance use is cessation, reductions in drug use and associated harms related to substance use have also been shown be effective in reducing HIV risk behaviors among drug using populations (Metzger et al., 1993, 2010; Ross et al., 2007; Rotheram-Borus et al., 2010). In addition, a high level of retention in this cohort study was achieved, with 93% being retained at the six-month visit. Lastly, the sample is geographically diverse and was recruited through venue-based sampling techniques, different from other longitudinal studies, which used word-of-mouth and convenience sampling (Warner et al., 2004; Wilson et al., 1999). It should be noted that women were not required to be a substance user to be eligible for the study, although substance use was one of several "personal risk characteristics" the women could have met to be included in the study; because of this, these substance use prevalence estimates may not be representative of women at high risk for HIV in general. However, our prevalence estimates do reveal a strikingly high level of substance use among women recruited from these diverse, yet impoverished locations that far exceed the general population, suggesting a critical need for interventions to reduce substance use problems among such women, given the demonstrated link between substance use and HIV risk.

In conclusion, a large proportion of low-income women recruited from communities deeply affected by HIV reported frequent engagement in drug use and binge drinking at the time of their participation in this study. It is clear that this population is in great need of effective interventions to reduce the burden of substance use and associated risk for HIV infection, including that from binge drinking. Although declines in the frequency of substance use over time were observed, this was only seen among those with a lower burden of substance use; a better understanding of the drivers of this decrease in use is needed in order to build culturally and gender-appropriate behavioral interventions. Further quantitative and qualitative data are critical to understand the patterns of substance use and factors associated with decision making regarding consumption and engaging in HIV risk.

Acknowledgments

The authors thank the study participants, community stakeholders, and staff from each study site. In particular, they acknowledge Lynda Emel, Jonathan Lucas, Nirupama Sista, Kathy Hinson, Elizabeth DiNenno, Ann O'Leary, Lisa Diane White, Waheedah Shabaaz-El, Quarraisha Abdool-Karim, Sten Vermund, Edward E. Telzak, Rita Sondengam, Cheryl Guity, Stephanie Lykes, Manya Magnus, Christopher Chauncey Watson, Kathleen Hatcher, Nicolette Vanterpool, Ilene Wiggins, Courtney Stachowski, Lynn Tillery, Shirley Brown, Carlos del Rio and Kathy Traylor, and Tom Coates for instrumental comments on the final draft. The lead author would also like to acknowledge the District of Columbia Developmental Center for AIDS Research (P30AI087714) for mentorship support.

Role of Funding Source: Nothing declared. Grant support provided by the National Institute of Allergy and Infectious Diseases, National Institute on Drug Abuse, and National Institute of Mental Health (cooperative agreement no. UM1 AI068619, U01-AI068613, and UM1-AI068613); Centers for Innovative Research to Control AIDS, Mailman School of Public Health, Columbia University (5U1Al069466); University of North Carolina Clinical Trials Unit (AI069423); University of North Carolina Clinical Trials Research Center of the Clinical and Translational Science Award (RR 025747); University of North Carolina Center for AIDS Research (AI050410);

Emory University HIV/AIDS Clinical Trials Unit (5UO1AI069418), Center for AIDS Research (P30 AI050409), and Clinical and Translational Science Award (UL1 RR025008); The Terry Beirn Community Programs for Clinical Research on AIDS Clinical Trials Unit(5UM1 AI069503-07) and; The Johns Hopkins Adult AIDS Clinical Trial Unit (AI069465) and The Johns Hopkins Clinical and Translational Science Award (UL1 RR 25005). The views expressed herein are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, the National Institutes of Health, the HPTN, or its funders.

References

Adimora AA, Schoenbach VJ, Martinson FE, Donaldson KH, Stancil TR, Fullilove RE. Concurrent partnerships among rural African Americans with recently reported heterosexually transmitted HIV infection. J Acquir Immune Defic Syndr. 2003; 34:423–429. [PubMed: 14615661]

Adimora AA, Schoenbach VJ, Taylor EM, Khan MR, Schwartz RJ. Concurrent partnerships, nonmonogamous partners, and substance use among women in the United States. Am J Public Health. 2011; 101:128–136. [PubMed: 20724694]

Boardman JD, Finch BK, Ellison CG, Williams DR, Jackson JS. Neighborhood disadvantage, stress, and drug use among adults. J Health Soc Behav. 2001; 42:151–165. [PubMed: 11467250]

Campbell, M.; Machin, D.; Walters, S. Medical Statistics. Wiley; New York: 2007.

Centers for Disease Control and Prevention. Estimated HIV incidence in the United States, 2007-2010. HIV Surveill Rep. 2012a; 17

Centers for Disease Control and Prevention. HIV Surveillance in Women. Atlanta, GA: 2012b.

Centers for Disease Control and Prevention. HIV Surveillance Report, 2011. Atlanta, GA: 2013.

Cohen DA, Mason K, Bedimo A, Scribner R, Basolo V, Farley TA. Neighborhood physical conditions and health. Am J Public Health. 2003; 93:467–471. [PubMed: 12604497]

Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry. 2007; 64:566–576. [PubMed: 17485608]

Corman H, Noonan K, Reichman NE, Dave D. Demand for illicit drugs among pregnant women. Adv Health Econ Health Serv Res. 2005; 16:41–60. [PubMed: 17867234]

D'Souza G, Matson PA, Grady CD, Nahvi S, Merenstein D, Weber KM, Greenblatt R, Burian P, Wilson TE. Medicinal and recreational marijuana use among HIV-infected women in the Women's Interagency HIV Study (WIHS) cohort, 1994-2010. J Acquir Immune Defic Syndr. 2012; 61:618–626. [PubMed: 23011399]

Dave D. The effects of cocaine and heroin price on drug-related emergency department visits. J Health Econ. 2006; 25:311–333. [PubMed: 16188336]

DiClemente RJ, Wingood GM, Crosby RA, Sionean C, Brown LK, Rothbaum B, Zimand E, Cobb BK, Harrington K, Davies S. A prospective study of psychological distress and sexual risk behavior among black adolescent females. Pediatrics. 2001; 108:E85. [PubMed: 11694669]

Dinenno EA, Oster AM, Sionean C, Denning P, Lansky A. Piloting a system for behavioral surveillance among heterosexuals at increased risk of HIV in the United States. Open AIDS J. 2012; 6:169–176. [PubMed: 23049666]

Edlin BR, Irwin KL, Faruque S, McCoy CB, Word C, Serrano Y, Inciardi JA, Bowser BP, Schilling RF, Holmberg SD. Intersecting epidemics--crack cocaine use and HIV infection among inner-city young adults. Multicenter Crack Cocaine and HIV Infection Study Team. N Engl J Med. 1994; 331:1422–1427. [PubMed: 7969281]

Friedman SR, Flom PL, Kottiri BJ, Zenilman J, Curtis R, Neaigus A, Sandoval M, Quinn T, Des Jarlais DC. Drug use patterns and infection with sexually transmissible agents among young adults in a high-risk neighbourhood in New York City. Addiction. 2003; 98:159–169. [PubMed: 12534420]

Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2007; 64:830–842. [PubMed: 17606817]

Hodder SL, Justman J, Hughes JP, Wang J, Haley DF, Adimora AA, Del Rio C, Golin CE, Kuo I, Rompalo A, Soto-Torres L, Mannheimer SB, Johnson-Lewis L, Eshleman SH, El-Sadr WM. HIV acquisition among women from selected areas of the United States: a cohort study. Ann Intern Med. 2013; 158:10–18. [PubMed: 23277896]

Hutton HE, McCaul ME, Chander G, Jenckes MW, Nollen C, Sharp VL, Erbelding EJ. Alcohol use, anal sex, and other risky sexual behaviors among HIV-infected women and men. AIDS Behav. 2012; 17:1694–1704. [PubMed: 22566077]

Jenness SM, Neaigus A, Hagan H, Murrill CS, Wendel T. Heterosexual HIV and sexual partnerships between injection drug users and noninjection drug users. AIDS Patient Care STDS. 2010; 24:175–181. [PubMed: 20214485]

Jones-Webb R, Snowden L, Herd D, Short B, Hannan P. Alcohol-related problems among black, Hispanic and white men: the contribution of neighborhood poverty. J Stud Alcohol. 1997; 58:539–545. [PubMed: 9273921]

Kuo I, Greenberg AE, Magnus M, Phillips G 2nd, Rawls A, Peterson J, Hamilton F, West-Ojo T, Hader S. High prevalence of substance use among heterosexuals living in communities with high rates of AIDS and poverty in Washington, DC. Drug Alcohol Depend. 2011; 117:139–144. [PubMed: 21316871]

Kuo WH, Wilson TE, Weber KM, Madhava V, Richardson J, Delapenha R, Des Jarlais D. Initiation of regular marijuana use among a cohort of women infected with or at risk for HIV in the Women's Interagency HIV Study (WIHS). AIDS Patient Care STDS. 2004; 18:702–713. [PubMed: 15659881]

Lillie-Blanton M, Stone VE, Snow Jones A, Levi J, Golub ET, Cohen MH, Hessol NA, Wilson TE. Association of race, substance abuse, and health insurance coverage with use of highly active antiretroviral therapy among HIV-infected women, 2005. Am J Public Health. 2010; 100:1493–1499. [PubMed: 19910347]

Logan TK, Leukefeld C. Sexual and drug use behaviors among female crack users: a multi-site sample. Drug Alcohol Depend. 2000; 58:237–245. [PubMed: 10759034]

Macalino GE, Celentano DD, Latkin C, Strathdee SA, Vlahov D. Risk behaviors by audio computer-assisted self-interviews among HIV-seropositive and HIV-seronegative injection drug users. AIDS Educ Prev. 2002; 14:367–378. [PubMed: 12413183]

McClelland RS, Sangare L, Hassan WM, Lavreys L, Mandaliya K, Kiarie J, Ndinya-Achola J, Jaoko W, Baeten JM. Infection with trichomonas vaginalis increases the risk of HIV-1 acquisition. J Infect Dis. 2007; 195:698–702. [PubMed: 17262712]

McLellan-Lemal E, O'Daniels CM, Marks G, Villar-Loubet O, Doherty IA, Simpson C, Weiss S, Hanna B, Adimora AA, White BL, Wheeling JT, Borkowf CB. Sexual risk behaviors among African-American and Hispanic women in five counties in the southeastern United States: 2008-2009. Womens Health Issues. 2012; 22:e9–18. [PubMed: 21784659]

Melchior L, Huba G, Brown V, Reback C. A short depression index for women. Educ Psychol Measure. 1993; 53:1117–1125.

Metzger DS, Koblin B, Turner C, Navaline H, Valenti F, Holte S, Gross M, Sheon A, Miller H, Cooley P, Seage GR 3rd. Randomized controlled trial of audio computer-assisted self-interviewing: utility and acceptability in longitudinal studies. HIVNET Vaccine Preparedness Study Protocol Team. Am J Epidemiol. 2000; 152:99–106. [PubMed: 10909945]

Metzger DS, Woody GE, McLellan AT, O'Brien CP, Druley P, Navaline H, DePhilippis D, Stolley P, Abrutyn E. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. J Acquir Immune Defic Syndr. 1993; 6:1049–1056. [PubMed: 8340896]

Metzger DS, Woody GE, O'Brien CP. Drug treatment as HIV prevention: a research update. J Acquir Immune Defic Syndr. 2010; 55(Suppl. 1):S32–36. [PubMed: 21045597]

Neaigus A, Jenness SM, Hagan H, Murrill CS, Wendel T. Reciprocal sex partner concurrency and STDs among heterosexuals at high-risk of HIV infection. J Urban Health. 2012; 90:902–914. [PubMed: 22729473]

Nijhawan AE, DeLong AK, Celentano DD, Klein RS, Sobel JD, Jamieson DJ, Cu-Uvin S. The association between trichomonas infection and incarceration in HIV-seropositive and at-risk HIV-

seronegative women. Sex Transm Dis. 2011; 38:1094–1100.10.1097/OLQ.0b013e31822ea147 [PubMed: 22082718]

NIMH Multisite HIV/STD Prevention Trial for African American Couples Group. Risky sexual behavior and correlates of STD prevalence among African American HIV serodiscordant couples. AIDS Behav. 2010; 14:1023–1031.10.1007/s10461-010-9698-8 [PubMed: 20499152]

Ober AJ, Iguchi MY, Weiss RE, Gorbach PM, Heimer R, Ouellet LJ, Shoptaw S, Anglin MD, Zule WA. The relative role of perceived partner risks in promoting condom use in a three-city sample of high-risk, low-income women. AIDS Behav. 2011; 15:1347–1358.10.1007/s10461-010-9840-7 [PubMed: 20976538]

Patrick ME, O'Malley PM, Johnston LD, Terry-McElrath YM, Schulenberg JE. HIV/AIDS risk behaviors and substance use by young adults in the United States. Prev Sci. 2012; 13:532–538.10.1007/s11121-012-0279-0 [PubMed: 22886042]

Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, Lin LS, An Q, Mermin J, Lansky A, Hall HI. Estimated HIV incidence in the United States, 2006-2009. PLoS One. 2011; 6:e17502. [PubMed: 21826193]

Prins A, Ouimette P, Kimerling R, Cameron R, Hugelshofer D, Shaw-Hegwer J, Thrailkill A, Gusman F, Sheikh J. The primary care PTSD screen (PC-PTSD): development and operating characteristics. Primary Care Psychiatry. 2003; 9:9–14.

Richards JE, Risser JM, Padgett PM, Rehman HU, Wolverton ML, Arafat RR. Condom use among high-risk heterosexual women with concurrent sexual partnerships, Houston, Texas, USA. Int J STD AIDS. 2008; 19:768–771. [PubMed: 18931271]

Ross MW, Timpson SC, Williams ML, Bowen A. The impact of HIV-related interventions on HIV risk behavior in a community sample of African American crack cocaine users. AIDS Care. 2007; 19:608–616. [PubMed: 17505921]

Rotheram-Borus MJ, Rhodes F, Desmond K, Weiss RE. Reducing HIV risks among active injection drug and crack users: the safety counts program. AIDS Behav. 2010; 14:658–668. [PubMed: 19757019]

Seth P, Wingood GM, DiClemente RJ, Robinson LS. Alcohol use as a marker for risky sexual behaviors and biologically confirmed sexually transmitted infections among young adult African-American women. Womens Health Issues. 2011; 21:130–135. [PubMed: 21276736]

Smith AM, Ferris JA, Simpson JM, Shelley J, Pitts MK, Richters J. Cannabis use and sexual health. J Sex Med. 2010; 7:787–793. [PubMed: 19694929]

Stein M, Herman DS, Trisvan E, Pirraglia P, Engler P, Anderson BJ. Alcohol use and sexual risk behavior among human immunodeficiency virus-positive persons. Alcohol Clin Exp Res. 2005; 29:837–843. [PubMed: 15897729]

Sterk CE, Theall KP, Elifson KW. Effectiveness of a risk reduction intervention among African American women who use crack cocaine. AIDS Educ Prev. 2003; 15:15–32. [PubMed: 12627741]

Stover CT, Smith DK, Schmid DS, Pellett PE, Stewart JA, Klein RS, Mayer K, Vlahov D, Schuman P, Cannon MJ. Group, H. I. V. E. R. S. Prevalence of and risk factors for viral infections among human immunodeficiency virus (HIV)-infected and high-risk HIV-uninfected women. J Infect Dis. 2003; 187:1388–1396.10.1086/374649 [PubMed: 12717619]

Theall KP, Scribner R, Ghosh-Dastidar B, Cohen D, Mason K, Simonsen N. Neighbourhood alcohol availability and gonorrhea rates: impact of social capital. Geospat Health. 2009; 3:241–255. [PubMed: 19440966]

Van Der Pol B, Kwok C, Pierre-Louis B, Rinaldi A, Salata RA, Chen PL, van de Wijgert J, Mmiro F, Mugerwa R, Chipato T, Morrison CS. Trichomonas vaginalis infection and human immunodeficiency virus acquisition in African women. J Infect Dis. 2008; 197:548–554. [PubMed: 18275275]

Warner LA, Alegria M, Canino G. Remission from drug dependence symptoms and drug use cessation among women drug users in puerto rico. Arch Gen Psychiatry. 2004; 61:1034–1041. [PubMed: 15466677]

Williams CT, Latkin CA. Neighborhood socioeconomic status, personal network attributes, and use of heroin and cocaine. Am J Prev Med. 2007; 32:S203–210. [PubMed: 17543712]

Wilson TE, Massad LS, Riester KA, Barkan S, Richardson J, Young M, Gurtman A, Greenblatt R. Sexual, contraceptive, and drug use behaviors of women with HIV and those at high risk for infection: results from the Women's Interagency HIV Study. Aids. 1999; 13:591–598. [PubMed: 10203384]

World Health Organization ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability, and feasibility. Addiction. 2002; 97:1183–1194. [PubMed: 12199834]

Table 1

Demographic characteristics and substance use in the past six months at baseline among women enrolled in HPTN 064 (N=1,882)

Baseline characteristics	Total N=1,882(%)	Frequent n=706(37%)	Non-frequent user n=726(39%)	Did not use n=450 (24%)	Chi-square p-value
Age (years)					<0.0001
18-24	612 (32.5%)	125 (17.7%)	268(36.9%)	219 (48.7%)	
25-35	676 (35.9%)	214 (30.3%)	304 (41.9%)	158 (35.1%)	
36+	594 (31.6%)	367 (52.0%)	154 (21.2%)	73 (16.2%)	
African American	1627 (86.5%)	602 (85.3%)	629 (86.6%)	396 (88.0%)	0.18
Latino/a or Hispanic origin	221 (11.7%)	87 (12.3%)	86 (11.8%)	48 (10.7%)	0.69
Less than high school education	683 (36.3%)	283 (40.1%)	244 (33.6%)	156 (34.7%)	0.03
Holdhold income					0.03
Refused to answer/Don't know	651 (34.6%)	258 (36.5%)	222 (30.6%)	171 (38.0%)	
$10,000 or less	842 (44.7%)	319 (45.2%)	325 (44.8%)	198 (44.0%)	
$10,001 to $20,000	208 (11.1%)	79 (11.2%)	91 (12.5%)	325 (44.8%)	
$20,001 or more	181 (9.6%)	50 (7.1%)	88 (12.1)	38 (8.4%)	
>1 partners (past 6 months)**	1095 (58.2%)	469 (66.4%)	422 (58.1%)	204 (45.3%)	
Concurrent partnership (self-reported)**	695 (36.9%)	339 (48.0%)	252 (34.7%)	104 (23.1%)	<0.0001
Had male partner who used drugs past 6 months	664 (35.3%)	390 (55.2%)	201 (27.7%)	73 (16.2%)	<0.0001
Used condom last vaginal sex**	327 (17.4%)	108 (15.3%)	120 (16.5%)	99 (22.0%)	0.01
Anal sex in past 6 months**	709 (37.7%)	321 (45.5%)	245 (33.7%)	143 (31.8%)	<0.0001
Exchanged sex for commodities *, **	680 (36.1%)	399 (56.5%)	203 (28.0%)	78 (17.3%)	<0.0001
Incarcerated in past 5 years	745 (39.6%)	369 (52.3%)	249 (34.3%)	127 (28.2%)	<0.0001
Depressive Symptoms**	626 (33.3%)	340 (48.2%)	199 (27.4%)	87 (19.3%)	<0.0001
Screened positive for post-traumatic stress disorder**	536 (28.5%)	271 (38.4%)	190 (26.2%)	75 (16.7%)	<0.0001
Injection drug use status**					<0.0001†
Never injector	1653 (87.8%)	564 (79.9%)	690 (95.0%)	399 (88.7%)	
Former injector (>6 months ago)	73 (3.9%)	49 (6.9%)	20 (2.8%)	4 (0.9%)	
Current injector (<=6 months ago)	73 (3.9%)	63 (8.9%)	10 (1.4%)	0 (0.0%)	

Baseline characteristics	Total N=1,882(%)	Frequent n=706(37%)	Non-frequent user n=726(39%)	Did not use n=450 (24%)	Chi-square p-value
Substance used in past 6 months					
Opioid	310 (16.5%)	254 (36.0%)	56 (7.7%)	0 (0.0%)	<0.0001†
Cocaine	471 (25.0%)	346 (49.0%)	125 (17.2%)	0 (0.0%)	<0.0001†
Amphetamines	203 (10.8%)	110 (15.6%)	93 (12.8%)	0 (0.0%)	0.11†
Sedative or Sleeping Pills	190 (10.1%)	145 (20.5%)	45 (6.2%)	0 (0.0%)	<0.0001†
Inhalants or Hallucinogens or other	81 (4.3%)	60 (8.5%)	21 (2.9%)	0 (0.0%)	<0.0001†
Binge drinking	1191 (63.3%)	564 (79.9%)	627 (86.4%)	0 (0.0%)	0.002†
Number of substances used					
0	450(23.9%)	0 (0.0%)	0 (0.0%)	450 (100.0%)	
1	808 (42.9%)	262 (37.1%)	546 (75.2%)	0 (0.0%)	
2	381 (20.2%)	244 (34.6%)	137 (18.9%)	0 (0.0%)	
3	143 (7.6%)	114 (16.1%)	29 (4.0%)	0 (0.0%)	
4+	100 (5.3%)	86 (12.2%)	14 (1.9%)	0 (0.0%)	
Mean number of substances used (SD)	1.3 (1.2)	2.1 (1.2)	1.3 (0.7)	0.0 (0.0)	<.0001†±

*Includes money, drugs, food, shelter, housing.

**Missing: Number of partners past 6 months: n=16 (0.9%); self-reported concurrency: n=6 (0.3%); used condom last vaginal sex: n=18 (1.0%); anal sex in past 6 months: n=2 (0.1%); exchanged sex for commodities: n=16 (0.9%); depressive symptoms: n=117 (6.2%); screened positive for post-traumatic stress disorder: n=28 (1.5%); injection drug use status: n=83 (4.4%).

†Non-user group was excluded for these p-values.

±T test used for p-value.

Table 2

Description of multiple substances used in the past six months among women in HPTN 064 at baseline (n=1,432)

	Opioid users N=310 (%)	Cocaine users N=471 (%)	Amphetamine users N=203 (%)	Sedative/ Sleeping Pill users N=190 (%)	Inhalant, hallucinogen, other users N=81 (%)	Binge drinkers N=1191 (%)
Other drugs used:						
Opioids	--	205 (43.5)	58 (28.6)	102 (53.7)	31 (38.3)	173 (14.5)
Cocaine	205 (66.1)	--	71 (35.0)	111 (58.4)	37 (45.7)	325 (27.3)
Amphetamines	58 (18.7)	71 (15.1)	--	63 (33.2)	28 (34.6)	170 (14.3)
Sedative or Sleeping Pills	102 (32.9)	111 (23.6)	63 (31.0)	--	34 (42.0)	147 (12.3)
Inhalants, Hallucinogens or Other	31 (10.0)	37 (7.9)	28 (13.8)	34 (17.9)	--	54 (4.5)
Binge drinking	173 (55.8)	325 (69.0)	170 (83.7)	147 (77.4)	54 (66.7)	--
Frequency of use						
Once or twice (or less than monthly)	74 (23.9)	150 (31.8)	122 (60.1)	84 (44.2)	33 (40.7)	429 (36.0)
Monthly	29 (9.4)	77 (16.3)	41 (20.2)	32 (16.8)	14 (17.3)	313 (26.3)
Weekly	38 (12.3)	105 (22.3)	23 (11.3)	37 (19.5)	12 (14.8)	288 (24.2)
Daily to less than weekly	169 (54.5)	139 (29.5)	17 (8.4)	37 (19.5)	22 (27.2)	161 (13.5)

Table 3

Bivariate associations of decreased substance use* from baseline to the six month visit in HPTN 064 (N=1,432)

Baseline Characteristics	Decreased use N=580	Did not decrease use N=852	RR for Decreased Use (95% CI)
Age (years) (vs 18-24)			
25 – 35	195 (33.6%)	323 (37.9%)	0.88 [0.75, 1.03]
36 +	216 (37.2%)	305 (35.8%)	0.96 [0.83, 1.12]
Race (vs non-African-American)			
African American	505 (87.1%)	726 (85.2%)	1.10 [0.91, 1.33]
Education (vs <high school)			
High school or higher	369 (63.6%)	536 (62.9%)	1.02 [0.89, 1.16]
Household income (vs. ≥$20,000)			
$10,000 or less	286 (49.3%)	358 (42.0%)	***1.28 [1.00, 1.63]***
$10,001 to $20,000	55 (9.5%)	115 (13.5%)	0.93 [0.68, 1.27]
Refused to answer/Don't know	191 (32.9%)	289 (33.9%)	1.14 [0.89, 1.47]
2+ partners in past 6 months (vs ≤1†)	351 (61.0%)	540 (64.1%)	0.93 [0.82, 1.05]
Concurrent partnership (self-reported)	232 (40.1%)	359 (42.3%)	0.95 [0.83, 1.08]
Had male partner who used drugs past 6 months	240 (41.4%)	351 (41.2%)	1.00 [0.88, 1.14]
Did not Use condom last vaginal sex	484 (84.3%)	705 (83.6%)	1.03 [0.87, 1.23]
Had anal sex in past 6 months	230 (39.7%)	336 (39.5%)	1.01 [0.88, 1.14]
Exchanged sex for commodities in past 6 months	242 (42.1%)	360 (42.7%)	0.99 [0.87, 1.12]
Incarcerated in past 5 years	252 (43.4%)	366 (43.0%)	1.01 [0.89, 1.15]
Depressive Symptoms	209 (38.5%)	330 (41.2%)	0.93 [0.82, 1.07]
Screened positive for post-traumatic stress disorder	177 (31.2%)	284 (33.8%)	0.93 [0.81, 1.07]
Substance used in past 6 months±			
Opioid	111 (19.1%)	199 (23.4%)	0.86 [0.73, 1.01]
Cocaine	177 (30.5%)	294 (34.5%)	0.90 [0.78, 1.03]
Amphetamines	78 (13.4%)	125 (14.7%)	0.95 [0.79, 1.15]
Sedative or Sleeping Pills	68 (11.7%)	122 (14.3%)	0.88 [0.72, 1.08]

Baseline Characteristics	Decreased use N=580	Did not decrease use N=852	RR for Decreased Use (95% CI)
Inhalants, Hallucinogens, or Other	36 (6.2%)	45 (5.3%)	1.12 [0.87, 1.44]
Binge drinking	476 (82.1%)	715 (83.9%)	0.94 [0.8, 1.11]
Number of substances used (vs 1)			
2 substances	145 (25.0%)	236 (27.7%)	0.88 [0.76, 1.02]
3 substances	54 (9.3%)	89 (10.5%)	0.87 [0.70, 1.09]
4+ substances	21 (5.3%)	69 (8.1%)	***0.72 [0.53, 0.97]***

RR = Relative Risk

* Decreased use based on reduced frequency of use of the substance used most frequently at baseline.

† Two women reported having zero male sex partners in the previous six months.

± Reference group = non-users of each particular drug.